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APPLICANT:	Kulkarni et al.	EXAMINER:	Cook, Rebecca
SERIAL NO.:	10/602,215	ART UNIT:	1614
FILED:	06/24/2003	PAPER NO.:	
FOR:	LIQUID PHARMACEUTICAL COMPOSITIONS		

DECLARATION UNDER 37 CFR § 1.132

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

I, Mei Cai, a permanent resident of the United States, residing at 7290 Andover Drive, Canton, MI, hereby declare:

1. I received a PhD degree in Analytical Chemistry from the University of Arizona in 1997. I received a BS degree in Chemistry from Peking University, China in 1990. I carried out post-doctoral studies at the University of Michigan between 1997 and 2000. I have authored or co-authored over 15 scientific articles/abstracts concerning pharmaceutical technology, surface chemistry, and separation science.

CERTIFICATE OF MAILING/TRANSMISSION (37 C.F.R. 1.8(a))

I hereby certify that, on the date shown below, this correspondence is being:

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2. I joined Pfizer Inc in 2001 as a Senior Scientist. I am currently a Principal Scientist in the Research Analytical Division of Pfizer Global Research and Development. I have carried out substantive analytical testing and research to support the development of active pharmaceutical ingredients and pharmaceutical dosage forms.

3. I have studied U.S. Patent Application No. 10/602,215, which is entitled "Liquid pharmaceutical compositions." The application describes liquid pharmaceutical compositions containing a GABA analog, such as gabapentin and pregabalin, and one or more polyhydric alcohols, such as xylitol and glycerol, that comprise at least 25% weight/volume (g/100mL) of the composition or from about 25% to about 75% weight/volume (w/v) of the composition. According to the patent application, the pH of each composition ranges from about 5.5 to about 7.0. The liquid pharmaceutical compositions may also include flavors and preservatives.

4. I have also studied International Patent Application No. WO 99/59573, which is entitled "Stabilized pharmaceutical preparations of gamma-aminobutyric acid derivatives and process for preparing same." I examined Example 2 on pages 58 and 59 of the application, which compares the stability of aqueous formulations containing gabapentin when stored at 45°C for at least one week. Example 2 shows that an aqueous formulation (sample e) containing 5% w/v gabapentin and 15% w/v xylitol exhibits greater lactam formation—0.311% w/w based on the initial amount of gabapentin—than an aqueous formulation (sample d) containing 5% w/v gabapentin and 0% xylitol. According to WO 99/59573, the greater lactam formation of sample e indicates that the formulation containing gabapentin and xylitol is less stable than the formulation containing gabapentin alone.

5. To examine the influence of pH and the presence of a polyhydric alcohol on lactam formation, a number of samples were prepared that contain water, gabapentin, and a polyhydric alcohol (xylitol or glycerol). The compositions of the samples are shown in Table 1, below. All of the samples contained 5% w/v gabapentin. Samples of formulation A contained no polyhydric alcohol. Samples of formulations B, C, D, and E

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contained 15%, 25%, 40%, and 75% w/v xylitol, respectively. Samples of formulations F, G, H, and I contained 15%, 25%, 40%, and 75% w/v glycerol, respectively. The initial pH of the samples was adjusted, when necessary, by adding an acid or base, and ranged from pH 3 to pH 9. In Table 1, the abbreviation "qs" indicates that a sufficient quantity of water was added to each sample to produce a liquid formulation having the indicated concentration of gabapentin and polyhydric alcohol.

6. In a manner similar to Example 2 of WO 99/59573, samples of liquid formulations A-I in Table 1 were subjected to stability testing at elevated temperature. Using a validated HPLC assay method, the amount of lactam in each sample was measured following 1, 2 or 3 weeks storage at 45°C. For each sample, the quantity of lactam was measured by comparing responses from the sample and a lactam reference standard. The amount of lactam was calculated as the percentage of lactam (mg) found in the sample relative to the amount of gabapentin (mg) in the original sample preparation.

7. Tables 2-4, below, list the amount of lactam present in the samples after storage at 45°C for 1, 2 or 3 weeks, respectively. The data indicate that aqueous compositions containing gabapentin exhibit improved stability when formulated at a pH of about 5.5 to about 7.0. See Table 2, formulations A, B and D. The data also indicate that aqueous gabapentin formulations containing a polyhydric alcohol generally exhibit improved stability over formulations that do not. Compare, e.g., formulations B-D, F and G in Table 2 with formulation A. Generally, the most improvement in stability occurs for formulations containing 15% w/v of polyhydric alcohol, but in some cases higher concentrations of polyhydric alcohol may have the same impact on stability as lower concentrations. Compare, e.g., formulations A, B and D in Table 2 having pH of 7.0.

8. The data in Tables 2, 3, and 4 indicate that pH plays an important role in lactam formation and suggest that sample e in Example 2 of WO 99/59573, which contained 5% w/v gabapentin and 15% w/v xylitol, was formulated at a pH outside the range of pH 6.0 to 7.3.

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9. I further declare that all statements made herein of my knowledge are true and that all statements made on information are believed to be true; and further that the statements were made with my knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001, Title 18 of the United States Code and that said willful false statements may jeopardize the validity of the application or any patent issued thereon.

29 Mar 2006
Date

Mei Cai
Mei Cai, PhD

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Table 1. Formulations A to I (g/100 mL)

	A	B	C	D	E	F	G	H	I
Gabapentin	5	5	5	5	5	5	5	5	5
Xylitol	0	15	25	40	75	0	0	0	0
Glycerol	0	0	0	0	0	15	25	40	75
Water	qs	qs	qs	qs	qs	qs	qs	qs	qs

Table 2. Lactam (mg lactam/mg gabapentin, %) of formulations A to I after storage for 1 week at 45°C

pH	A	B	C	D	E	F	G	H	I
3.0	7.661								
5.0	0.636	0.736		0.797					
5.5	0.329	0.343		0.432					
6.0	0.146	0.166		0.197					
6.5	0.182	0.130	0.146	0.168	0.221	0.146	0.166	0.200	0.322
7.0	0.312	0.229		0.225					
7.3	0.403	0.162		0.276					
9.0	5.951								

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Table 3. Lactam (mg lactam/mg gabapentin, %) of formulations A to I after storage for 2 weeks at 45°C

pH	A	B	C	D	E	F	G	H	I
3.0	15.035								
5.0	1.272								
5.5	0.668	0.677		0.856					
6.0									
6.5	0.364	0.255	0.287	0.328	0.459	0.298	0.332	0.392	0.646
7.0	0.611								
7.3	0.821	0.338		0.505					
9.0	11.925								

Table 4. Lactam (mg lactam/mg gabapentin, %) of formulations A to I after storage for 3 weeks at 45°C

pH	A	B	C	D	E	F	G	H	I
3.0	22.209								
5.0	2.096								
5.5									
6.0									
6.5	0.537	0.396	0.434	0.496	0.705	0.449	0.509	0.617	1.029
7.0	0.906								
7.3									
9.0	17.613								

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